work with its large cadre of molecular motors is associated with many if not most other cell constituents and enzymes. Thus, a wide variety of enzyme systems are likely to feel transient loads that could have dramatic effects on their biochemical behaviors. As in the past, a detailed understanding of molecular motors provides us with insights into how proteins in general are able to achieve their remarkable and diverse activities.

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CK2 and PML: Regulating the Regulator

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The PML protein induces senescence, and, upon oncogenic stress, its absence promotes cellular transformation. In this issue of *Cell*, Scaglioni et al. (2006) show that phosphorylation of PML by CK2, a kinase frequently activated in human cancers, promotes PML degradation. Therefore, pharmacological inhibition of CK2-induced PML loss could be used to offset tumor establishment.

Analysis of the chromosomal translocations in tumor cells from acute promyelocytic leukemia patients led to the discovery of the *PML* gene. Fusion between the retinoic acid receptor α gene (*RARα*) and several other genes, most frequently *PML*, results in the production of chimeric proteins that drive the uncontrolled cellular proliferation and block in differentiation that leads to leukemia. Interestingly, the PML protein accumulates in subnuclear domains termed PML nuclear bodies, the function of which has remained a puzzle to cell biologists. Despite the fact that *Pml*-deficient mice exhibit only subtle defects, a variety of biological functions have been assigned to PML, ranging from senescence and apoptosis to combating viral infection. The many biochemical processes (such as transcription, DNA repair, and proteolysis) proposed to be under PML control add to the mystery surrounding this protein.

In this issue of *Cell*, Scaglioni et al. (2006) demonstrate that casein kinase 2 (CK2), a kinase associated with cancer promotion, phosphorylates PML and targets it for degradation by the proteasome. Loss of the critical CK2 phosphorylation site in PML results in stabilization of this protein, enhancement of PML-induced apoptosis and senescence, and abrogation of sensitivity to CK2 inhibitors. Moreover, in human non-small cell lung cancers, there is an inverse relationship between PML expression and CK2 activity. PML degradation upon CK2 activation could account for the frequent loss of PML expression observed in multiple human tumors. This loss of PML could promote tumor formation because the enforced expression of activated Ras (which leads to cancer) induced more aggressive lesions in the lungs of *Pml*-deficient mice compared to wild-type animals (Scaglioni et al., 2006). PML is upregulated during senescence and is also required for the induction of senescence caused by Ras activation or PTEN loss ex vivo and in vivo (Scaglioni et al., 2006; Trotman et al., 2006). Similarly, PML overexpression in primary fibroblasts is sufficient to trigger senescence (Bischof et al., 2002). CK2 activation could thus inhibit oncogene-induced senescence by mediating PML loss. Hence, *PML* transcriptional induction by growth-suppressive pathways (such as the interferon, p53, or TGF-β signaling pathways) may be balanced by

PML protein degradation through the activity of stress-activated kinases such as p38-MAPK or CK2, resulting in modulation of senescence at the early stages of neoplastic transformation. These results raise fascinating prospects for direct pharmacologic control of PML abundance through inhibition of CK2 or proteasome activity.

How does PML exert its many effects mechanistically? Several models have been proposed. The structural model assumes that a major function of PML is to recruit proteins into nuclear bodies. Concentration of these proteins within discrete nuclear domains could result in their sequestration, facilitate interactions, or allow posttranslational modifications to occur. Sequestration of proteins into PML nuclear bodies could have important functional consequences, such as in the case of Daxx, where sequestration interferes with its ability to act as a transcriptional repressor (Negorev and Maul, 2001). Yet, to date, only limited evidence has emerged demonstrating the impact of protein sequestration in these bodies. An example of a posttranslational modification that occurs in PML nuclear bodies is the inactivation of nuclear phospho-Akt. PML recruits the activated Akt kinase together with its cognate phosphatase PP2aC into nuclear bodies, thereby facilitating dephosphorylation of Akt. This results in removal of activated phospho-Akt from the nucleus (Trotman et al., 2006). This structural model, however, cannot apply to all properties assigned to PML, as the induction of senescence and modulation of TGF-β signaling appear to be independent of PML localization to nuclear bodies (Bischof et al., 2002; Lin et al., 2004).

A second important area of research associated with PML is sumoylation. PML is efficiently sumoylated, and several of its properties—including binding to MDM2, degradation by viruses and arsenic trioxide, and transformation by PML-RARα—are directly linked to one of its three sumoylation sites (Wei et al., 2003; Zhu et al., 2005). Moreover, many proteins that accumulate in PML nuclear bodies can themselves undergo sumoylation, and their recruitment into PML nuclear bodies requires the same critical sumoylation site in PML. Intriguingly, the CK2 phosphorylation site controlling PML degradation identified by Scaglioni et al. (2006) is located within a recently identified SUMO-interacting motif (SIM) (Hecker et al., 2006), a short sequence that interacts noncovalently with different SUMO isoforms. CK2-mediated PML phosphorylation could thus modulate the function of this domain, which may contribute to the degradation process. A fine dissection of PML sumoylation could therefore bring important insights into PML function.

The last model is an enzymatic one. PML belongs to the RBCC/TRIM family of proteins, many of which are E3 ubiquitin ligases whose activities depend on the integrity of the RING finger, an important motif in the ligase domain of these enzymes (Meroni and Diez-Roux, 2005). Analysis of a PML RING-finger mutant in vivo could lend some support to the hypothesis that ubiquitin ligase activity is essential for PML function. No putative substrates of PML-mediated ubiquitylation have been identified to date. Nevertheless, ubiquitin, proteasome components, and many short-lived proteins have been detected in PML nuclear bodies, particularly after proteasome inhibition, arguing for some connection between PML nuclear bodies and proteolysis.

Other RBCC/TRIM proteins have been proposed to have a scaffolding function in addition to their E3 ligase activity. Furthermore, the nuclear or cytoplasmic macromolecular structures that they have been shown to organize are proposed to represent niches specialized in posttranslational modifications (Meroni and Diez-Roux, 2005). In the case of PML, the RING finger is required for the formation of PML nuclear bodies, PML sumoylation, and recruitment of proteins, emphasizing the interdependence between the three models outlined above. Although endogenous PML is expressed as a variety of C-terminal splice variants, most previous studies have used the single variant that triggers senescence. Yet it was recently demonstrated that the most abundant PML species in primary cells have not been the focus of significant attention (Condemine et al., 2006). Exciting new developments are likely to come in this field, but regardless of the biochemical mechanism underlying PML function, the tight control of PML abundance by CK2 described by Scaglioni et al. (2006) is likely to be a significant piece of the puzzle.

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